[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

Quinazolines and 1,4-Benzodiazepines. III.[1] Substituted 2-Amino-5-phenyl-3H-1,4-benzodiazepine 4-Oxides

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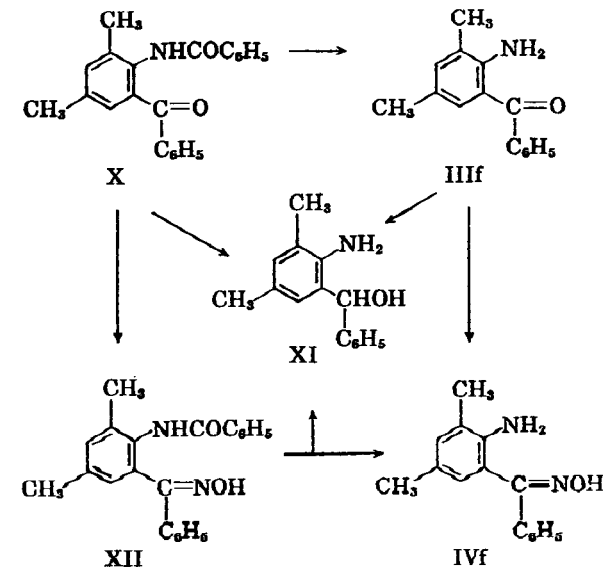
On treatment with methylamine, substituted 2-chloromethyl-4-phenylquinazoline 3-oxides (V) undergo rearrangement to yield the corresponding 2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxides (VI). In a few cases also the unrearranged 2-methylaminomethyl-4-phenylquinazoline 3-oxides (VII) were isolated. Some of the benzodiazepine 4-oxides were converted into the corresponding benzodiazepines (VIII) by treatment with phosphorus trichloride. Many of the benzodiazepines and their oxides show interesting sedative, muscle relaxant, and anticonvulsant properties in animals.

In view of the interesting pharmacological[2] properties of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 3-oxide hydrochloride[3] and its homologs,[1] a number of related compounds were synthesized. These compounds were prepared as shown below from *o*-aminobenzophenones (III) bearing various substituents in the phenyl rings A and B.

Most of the ketones III used as starting material were known and were prepared as described in the literature[4] with the exception of the ketones shown in Table I (IIIa–e)[5] which are new.

These ketones were prepared by condensing *p*-substituted anilines bearing in some cases additional substituents (yielding ring A of the benzophenone) and benzoyl chloride or a substituted benzoyl chloride (yielding ring B) using zinc chloride as catalyst. The intermediate reaction products of the



(1) Paper II. L. H. Sternbach, and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1960).

(2) L. O. Randall, W. Schallek, G. Heise, E. F. Keith, and R. Bagdon, *J. Pharm. and Exp. Ther.*, 129, 163 (1960).

(3) The generic name of this compound is chlordiazepoxide and it is marketed under the trade name Librium.®

(4) IIIh: J. Chattaway and J. Lewis, *J. Chem. Soc.*, 85, 589 (1904). IIIi: J. Angel, *J. Chem. Soc.*, 101, 515 (1912). IIIj,k: Ger. Patent 630,021, 1936: G. Kränzlein and Th. Meissner, *Friedländer*, 23, 234 (1936). III l,g: F. Ullmann and H. Bleier, *Ber.*, 25, 4273 (1902). IIIm: F. Ullmann and W. Denzler, *Ber.*, 39, 4332 (1906).

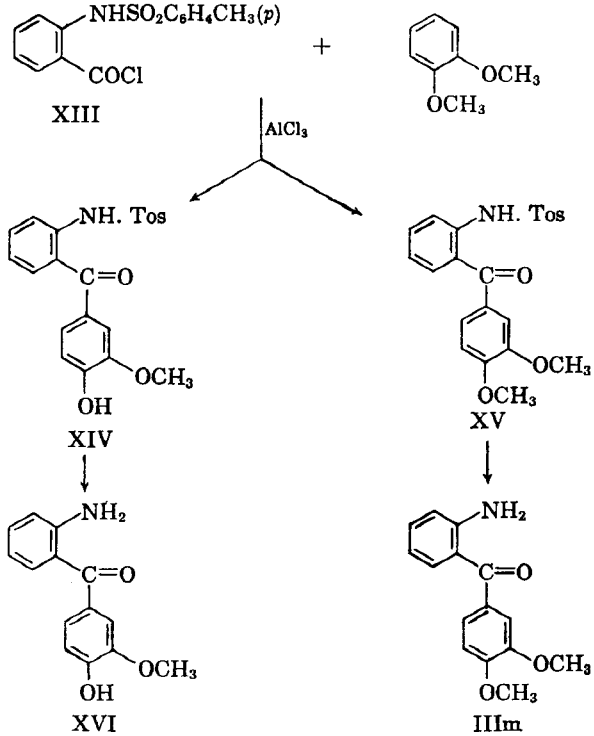
(5) The same letters signify throughout compounds bearing the same substituents in rings A and B. This refers also to the known ketones mentioned in ref. 4. All substituents are shown in Table IV.

structure II[6] were, without isolation, split by energetic acid hydrolysis to yield the desired products III (methods A and B).

Compound IIIb was also prepared by chlorination of 2-acetamido-5-chlorobenzophenone, followed by hydrolytic removal of the acetyl group (method C). One of these ketones (IIIf) had formerly been described as a product of the alkaline hydrolysis of the corresponding benzoyl derivative (X).[6]

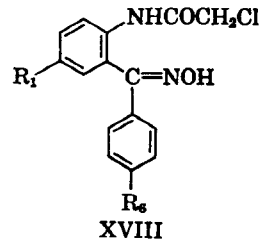
It was found, however, that the colorless compound (m.p. 128.5°) formerly described as IIIf was the benzhydrol XI formed during the energetic hydrolysis of X with alcoholic alkali.[7] We proved this by its formation on catalytic hydrogenation of the ketone IIIf (yellow plates, m.p. 68–70°) which we obtained by energetic acid hydrolysis of X.

On preparing the 3′,4′-dimethoxy-2-*p*-toluenesulfonamidobenzophenone (XV) as described in the literature,[4] we observed the simultaneous formation of 4′-hydroxy-3′-methoxy-2-(*p*-toluenesulfonamido) benzophenone (XIV)[8] formed because of the demethylating effect of aluminum chloride. This compound was hydrolyzed to 2-amino-4′-hydroxy-3′-methoxybenzophenone (XVI) which yielded on methylation with diazomethane the desired known 2-amino-3′,4′-dimethoxybenzophenone (IIIm).



The oximes IV were prepared from the corresponding ketones by heating with hydroxylamine hydrochloride in alcohol or in a mixture of alcohol and pyridine.[9] The methods of preparation and other data are shown on table II.[11] The oxime IVf was also prepared from XII by alkaline hydrolysis.

The conversion of the oximes into the corresponding chloromethylquinazoline 3-oxides V[10] (Table III) was carried out by treatment with chloroacetyl chloride combined in some cases with the introduction of gaseous hydrogen chloride. In one case (Method H) the reaction product was isolated as the hydrochloride.[12] For the preparation of Ve (Method G) the chloroacetyl derivative XVIIIe was prepared as an intermediate. In another case the analogous compound XVIIIl was isolated as by-product (Method H).



XVIII

e. R_1 = Br; R_6 = CH_3.
l. R_1 = H; R_6 = OCH_3.

The chloromethylquinazoline 3-oxides V on treatment with methylamine[13] underwent in most cases a ring enlargement and yielded the benzodiazepine 4-oxides VI,[1] shown in Table IV.

In some cases also the normal reaction products, the quinazoline 3-oxides (VIIh, j, k) shown on Table V were isolated.[14,15] Only in one case no rearrangement at all could be observed and only the normal reaction product (Vf→VIIf) was isolated.

(6) K. Dziewoński and L. H. Sternbach, *Bull. intern. acad. Polonaise, Classe Sc. math. nat. Ser. A*, 333 (1935); *Chem. Abstr.* 30, 2972 (1936).

(7) Benzophenone can be converted into benzhydrol on treatment with alkali in alcohol at 160°. See for instance A. Zagoumenny, *Ann.*, 184, 163 (1876).

(8) The negative indo-aniline test [D. E. Janssen, J. Van Allan, and C. V. Wilson, *J. Org. Chem.*, 20, 1326 (1955); D. W. Vittum and G. H. Brown, *J. Am. Chem. Soc.*, 68, 2235 (1946)] suggests that the free hydroxyl group is in position 4′.

(9) In two cases both the α- and β-oximes were isolated (b and e); in all other cases only the α-oximes were isolated. See paper I of this series,[10] footnote 9.

(10) Paper I of this series: L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, 82, 475 (1960).

(11) The oximes IVg and IVk are known. See K. Auwers and F. v. Meyenburg, *Ber.*, 24, 2370, 2383, 2385 (1891) and paper I[10] of this series.

(12) The hydrochlorides are stable only in the absence of water as the compounds V are very weak bases.

(13) In one case (Vi) also ammonia and ethylamine, respectively, were used for the reaction, and the corresponding amino- and ethylaminobenzodiazepine 4-oxides were obtained.

(14) Since no particular attempts were made to isolate products of this type, it is quite possible that also in other cases smaller amounts of the not rearranged products were formed.

(15) The structure of these compounds was correlated *via* their infrared and in some cases also *via* their ultraviolet spectra. See paper II of this series, footnote 2.[1]

The mechanism of this rearrangement has not yet been elucidated. It has, however, been found that the presence of an electron-releasing methyl group in position 6 (R_1) of the quinazoline nucleus in compounds V favors the formation of the unrearranged product VII. An additional methyl group in 8 (R_3) enhances this effect so that in the case of the 6,8-dimethylquinazoline derivative Vf only the normal, unrearranged product VIIf could be isolated.

Some of the benzodiazepines were characterized by their acetyl derivatives IX (Table IV) which were prepared by treatment with acetic anhydride in pyridine. The position of the acetyl group on the exocyclic nitrogen (not in position 1) was proved as will be discussed in a forthcoming paper.

Some benzodiazepine 4-oxides VI were converted into the corresponding "desoxy derivatives" VIII (Table VI) by treatment with phosphorus trichloride.

The hydrochlorides of VI and VII were tested in our Pharmacology Department by Dr. L. O. Randall and his co-workers. Most of the benzodiazepine 4-oxides showed interesting muscle relaxant, sedative, and anticonvulsant properties.

EXPERIMENTAL[16]

All melting points are corrected. The infrared and ultraviolet absorption spectra of starting materials and reaction products were compared wherever necessary in order to establish structural changes. The infrared spectra were determined in 1–5% chloroform solutions using a Perkin Elmer Model 21 spectrophotometer, the ultraviolet absorption spectra in isopropyl alcohol and in 0.1*N* hydrochloric acid.

2-Aminobenzophenones (III, Table I). *Method A.* To 3.5 moles of the benzoyl chloride heated to 120° was added in portions with stirring 1.4 moles of the *p*-substituted aniline. The mixture was then heated to 180–200° and 230 g. of zinc chloride was added. The temperature was gradually increased to 220–230° and kept there until the hydrogen chloride evolution had ceased (1–2 hr). After cooling to 120°, water was cautiously added and the mixture stirred and heated to reflux. The hot water layer was decanted and this procedure repeated two or three times. The water-insoluble brown mass was finally dissolved in a boiling mixture of 350 ml. of water, 500 ml. of acetic acid and 650 ml. of concd. sulfuric acid. The solution was refluxed for 17 hr. and then, after cooling, poured into a large amount of ice water. The reaction product was extracted with ether, separating it thus from the acid-soluble[17] *p*-substituted aniline, formed from compound II. The ether solution was then washed with an excess of alkali to remove the benzoic acid, dried, and concentrated to a small volume. The residue was recrystallized and yielded the reaction product forming yellow crystals.

Method B. The hydrolysis was done using *ca.* 2 l. of a 2:1 mixture of glacial acetic and concentrated hydrochloric acids, and the solution was concentrated *in vacuo* before dilution with ice water. The other steps were carried out as under A.

2-Amino-3,5-dichlorobenzophenone (IIIb, Table I). *Method C.* A solution of 60.2 g. (0.22 mole) of 2-acetamido-5-chlorobenzophenone in a mixture of 137 cc. of acetic acid and 82 cc. of nitric acid was saturated with hydrogen chloride. The mixture was left at room temperature for 1 hr. and was then diluted with water and extracted with methylene chloride. The methylene chloride solution was washed with water, dried, and concentrated *in vacuo*. The residue was dissolved in ether and crystallized by the addition of petroleum ether (b.p. 30–60°). The 2-acetamido-3,5-dichlorobenzophenone thus obtained (*ca.* 50% yield) formed colorless prisms melting at 143–144°.

Anal. Calcd. for $C_{15}H_{11}O_2NCl$: C, 58.46; H, 3.59; Cl, 23.01. Found: C, 58.96; H, 3.87; Cl, 23.02.

This compound was hydrolyzed to the aminobenzophenone as follows. A mixture of 72 g. of 2-acetamido-3,5-dichlorobenzophenone, 600 cc. of alcohol and 600 cc. of concd. hydrochloric acid was refluxed for 3 hr., then diluted with ice, made alkaline, and extracted with ether. The ether solution was dried and concentrated, giving a practically quantitative yield of the desired product.

2-Amino-3,5-dimethylbenzhydrol (XI). A mixture of 20 g. of 2-benzamido-3,5-dimethylbenzophenone (X)[7] 30 g. of potassium hydroxide, 30 cc. of water, and 170 cc. of alcohol was heated in an autoclave for 5 hr. to 170°. The reaction mixture was then diluted with water and extracted with ether. The ether extract was dried and partly concentrated *in vacuo* yielding 1.9 g. of colorless crystals.[18] After recrystallization from ether, the product formed fine colorless needles melting at 124–125°. The infrared spectrum shows the typical hydroxyl band at 3620 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.29; H, 7.54; N, 6.31. Found: C, 79.46; H, 7.19; N, 6.09.

The same compound was obtained on catalytic hydrogenation with 1 mole of hydrogen of 2-amino-3,5-dimethylbenzophenone (IIIf) at room temperature using prehydrogenated platinum oxide as catalyst and 80% acetic acid as solvent.

N,O-Diacetyl derivative. A solution of 2 g. of the aminobenzhydrol in a mixture of 5 cc. of acetic anhydride and 5 cc. of pyridine was left at room temperature for 20 hr. and concentrated *in vacuo*. The residue was crystallized from a mixture of acetone, ether and petroleum ether. The product formed fine needles melting at 149–150°.

Anal. Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.40; H, 6.94; N, 4.59.

2-(p-Toluenesulfonamido)-3',4'-dimethoxybenzophenone[19] (XV) *and 2-(p-toluenesulfonamido)-4'-hydroxy-3'-methoxybenzophenone* (XIV).[20] A mixture of 135 g. of *p*-toluenesulfonylanthranilic acid, 108 g. of phosphorus pentachloride and 1.35 l. of carbon disulfide was stirred and refluxed until complete solution occurred (45 min). To the cooled solution was added 90 g. of veratrole; then 270 g. of aluminum chloride (anhydrous, sublimed, reagent grade) was introduced as quickly as possible (hydrogen chloride and heat evolution). The mixture was then stirred and refluxed for 20 min. The carbon disulfide layer was decanted and the residual dark resinous complex decomposed with ice and hydrochloric acid. The organic material was dissolved in methylene chloride, the organic solution was washed with water, and then extracted with 3*N* potassium hydroxide. The alkaline solution containing the reaction products was acidified and extracted with benzene. The benzene solution was dried, and partly concentrated *in vacuo* to yield several fractions of crystals (55 g.) melting between 132 and 138°. In other reactions smaller amounts of mixtures were obtained which melted around 110° and contained the dimethoxy derivative reported in the literature.[19] A fraction melting at 136–138° yielded, after recrystallization from a mixture of ether and

(16) In part with B. Brust and C. Mason.

(17) The *o*-aminobenzophenone is not basic enough to dissolve in dilute mineral acid.

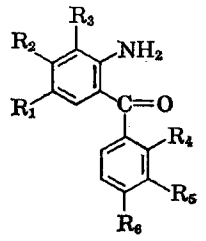
(18) The mother liquor contains 2-amino-3,5-dimethylbenzophenone.

(19) F. Ullmann and W. Denzler, *Ber.*, **39**, 4332 (1906). The pure dimethoxy derivative melts at 125°.

(20) With the cooperation of Mr. A. Henninger.

TABLE I[a]

o-AMINOBENZOPHENONES (III)

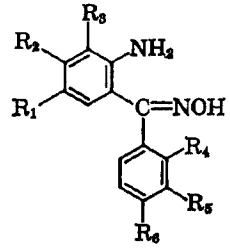


	R_1	R_2	R_3	R_4	R_5	R_6	Method	Cryst. from	Crystal Shape	M.P.	Yield,[b] %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
a	Cl	Cl					B	C_2H_5OH, Pet.[c]	Prisms	107–18°	39	$C_{13}H_9NOCl_2$	58.67	3.41	58.61	3.62
b	Cl		Cl				A	Eth.	Prisms	93–94°	40	$C_{13}H_9NOCl_2$	58.67	3.41	58.84	3.50
							C	Pet.								
c[d]	Cl					Cl	B	C_2H_5OH	Needles	118–119°	36	$C_{13}H_9NOCl_2$	58.67	3.41	58.78	3.13
d	Cl			Cl			A[e]	Eth.	Prisms	88–89°	80	$C_{13}H_9NOCl_2$	58.67	3.41	58.78	3.50
								Pet.								
e	Br					CH_3	A	Benzene, Pet.	Plates	105–106°	52	$C_{14}H_{12}ONBr$	57.95	4.17	57.60	4.20
f[f]	CH_3		CH_3				A	Pet.	Plates	68–70°	40	$C_{15}H_{15}ON$	79.97	6.71	79.98	6.70

[a] Only substituents other than hydrogen are shown under R_1–R_6. [b] The yield calculation is based on the substituted aniline and takes into consideration the formation of the quinazoline derivative II which allows only one-half of the aniline to be converted into the corresponding benzophenone. Some of these experiments were carried out only once. Changes in the reaction conditions might therefore result in considerably higher yields. [c] Pet. = petroleum ether, b.p. 30–60°. [d] This ketone was first synthesized by Mr. L. A. Dolan. [e] In this case the hydrolysis was also attempted according to method B and resulted in the formation of a mixture of the aminobenzophenone and 2-(*o*-chlorobenzamido)-2′,5-dichlorobenzophenone. The latter compound was separated by fractional crystallization from ether in which it is less soluble than the free amine. It forms colorless needles melting at 136–137°. *Anal.* Calcd. for $C_{20}H_{12}Cl_3NO_2 \cdot C$: C, 59.36; H, 2.99; Cl, 26.28; N, 3.46. Found: C, 59.67; H, 3.39; Cl, 26.13; N, 3.49. [f] This compound was prepared by hydrolysis for four hours of compound X according to Method A.

TABLE II[a]

o-AMINOBENZOPHENONE OXIMES (IV)

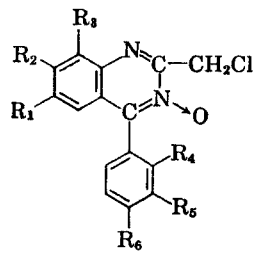


	R_1	R_2	R_3	R_4	R_5	R_6	Method	Cryst. from	Color, Shape	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
a	Cl	Cl					D	Eth.[b]-Pet.	Colorless crystals	150–151°	70	$C_{13}H_{10}N_2OCl_2$	55.53	3.59	55.92	3.60
b	Cl		Cl				D	α dil. C_2H_5OH	Flat needles	126–127°	68	$C_{13}H_{10}N_2OCl_2$	55.53	3.59	α55.37	3.71
								β Eth.-Pet.	Yellow needles	122–123°					β55.43	3.73
c	Cl					Cl	E	Benz.-Pet.	Colorless prisms	151–154°	65	$C_{13}H_{10}N_2OCl_2$	55.53	3.59	55.64	3.64
d	Cl			Cl			D[c]	Benz.-Pet.	Colorless crystals	137–139°	16	$C_{13}H_{10}N_2OCl_2$	55.53	3.59	55.75	3.54
e	Br					CH_3	E	α Eth.	Colorless Prisms	204–205°	64	$C_{14}H_{13}N_2OBr$	55.10	4.29	α54.95	4.53
								β Benz.-Pet.	Colorless Needles	115–116°	25				β55.43	4.30
f[11]	CH_3		CH_3				D	Eth.-Pet.	Colorless prisms	141–142°	65	$C_{15}H_{16}ON_2$	74.97	6.71	74.74	6.51
h	CH_3						D	Eth.	Colorless needles	189–191°	76	$C_{14}H_{14}N_2O$	74.31	6.24	74.36	6.01
i	Br						D	Eth.	Colorless prisms	192–193°	57	$C_{13}H_{11}N_2OBr$	53.63	3.80	53.96	4.07
j[11]	CH_3	CH_3				Cl	D	Eth.-Pet.	Colorless needles	156–157°	83.6	$C_{15}H_{15}N_2OCl$	65.57	5.50	65.80	5.63
						OCH_3	D	CH_3OH	Colorless prisms	123–126°	70	$C_{14}H_{14}N_2O_2$	69.40	5.83	68.98	5.66
m					OCH_3	OCH_3	D	Eth.	Colorless prisms	162–163°	62	$C_{15}H_{16}N_2O_3$	66.16	5.92	66.06	5.75

[a] Only substituents other than hydrogen are shown under R_1–R_6. [b] Eth. = ether, pet. = petroleum ether, b.p. 30–60°, benz. = benzene. [c] In this case, only pyridine containing 1% of piperidine was used as solvent. The oxime which formed in small yield due to steric hindrance was separated from the unchanged acid insoluble aminobenzophenone by extraction with 2*N* hydrochloric acid.

TABLE III[a]

CHLOROMETHYLQUINAZOLINE *N*-OXIDES (V)

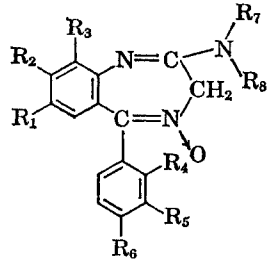


	R_1	R_2	R_3	R_4	R_5	R_6	Method	Cryst. from	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
a	Cl	Cl					F[b,c]	CH_2Cl_2 Eth.-Pet.[d]	159–160°	72.2	$C_{15}H_9N_2OCl_3$	53.05	2.67	53.11	2.64
b	Cl		Cl				F[b]	CH_2Cl_2 Pet.	185–186°	44	$C_{15}H_9N_2OCl_3$	53.05	2.67	53.35	3.20
c	Cl					Cl	F[a,e]	CH_2Cl_2 Pet.	163–164°	82	$C_{15}H_9N_2OCl_3$	53.05	2.67	52.99	2.79
d	Cl			Cl			F[f]	CH_2Cl_2 Pet.	140–143°	71	$C_{15}H_9N_2OCl_3$	53.05	2.67	52.94	2.53
e	Br					CH_3	G	CH_2Cl_2 Pet.	162–164°	25	$C_{16}H_{12}N_2OClBr$	52.84	3.33	53.24	3.25
f	CH_3		CH_3					CH_2Cl_2 Pet.	179–185°	72	$C_{17}H_{15}N_2OCl$	68.34	5.06	68.83	5.03
g							F	CH_2Cl_2 Pet.	160–161°	76	$C_{15}H_{11}N_2OCl$	66.55	4.10	66.21	4.06
h	CH_3						F[b,c]	CH_2Cl_2 Eth.	152–153°	80	$C_{16}H_{13}N_2OCl$	67.49	4.60	67.28	4.50
i	Br						F[b]	Ac.[d]	189–190°	84	$C_{15}H_{10}N_2OBrCl$	51.53	2.88	51.76	2.73
j[g]	CH_3	CH_3				Cl	F	Ac.	192–193°	76	$C_{17}H_{14}N_2OCl_2$	61.27	4.24	61.42	3.96
l						OCH_3	H	CH_2Cl_2	179–180°	57	$C_{16}H_{13}N_2O_2Cl$	63.90	4.36	63.66	4.42
m					OCH_3	OCH_3	F[h]	Ac.-Eth.	138–139°	48	$C_{17}H_{15}N_2O_3Cl$	61.73	4.57	62.26	4.84

[a] Only substituents other than hydrogen are shown under R_1–R_6. [b] The saturation with HCl was omitted. [c] The solution was heated to 60° for 30 min. [d] Eth. = ether, pet. = petroleum ether, b.p. 30–60°, ac. = acetone. [e] Because of the low solubility of the starting material, the 15-fold amount (instead of the 6-fold) of glacial acetic acid was used. [f] In this case 3 moles of chloroacetyl chloride was used and hydrogen chloride was introduced for 5 hr. at 80°. [g] Vk is known.[10] [h] Only 1.1 moles of chloroacetyl chloride was used.

TABLE IV[a]

BENZODIAZEPINE *N*-OXIDES(VI) AND ACETYL DERIVATIVES(IX)



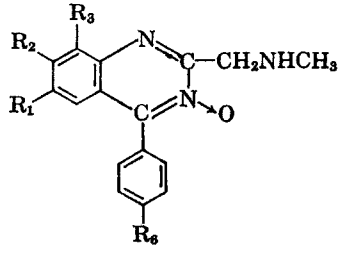
	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Method	Cryst. from[b]	Color, Shape	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
a	Cl	Cl					CH_3		J	CH_3OH	Yellowish prisms	233–234°	*ca.* 100	$C_{16}H_{13}N_3OCl_2$	57.50	3.92	57.44	3.97
a·HCl[c]	Cl	Cl					CH_3		L	CH_3OH Eth.-pet.	Colorless plates	231–232°		$C_{16}H_{13}N_3OCl_2$·HCl	51.84	3.81	51.91	3.76
b	Cl		Cl				CH_3		J	CH_3OH	Yellowish prisms	251–252°	71	$C_{16}H_{13}N_3OCl_2$	57.50	3.92	57.43	3.70
b·HCl	Cl		Cl				CH_3		L	C_2H_5OH	Colorless crystals	204–207°		$C_{16}H_{13}N_3OCl_2$·HCl	51.84	3.81	52.57	3.92
c	Cl					Cl	CH_3		J	C_2H_5OH	Yellowish prisms	254–255°	68	$C_{16}H_{13}N_3OCl_2$	57.50	3.92	57.03	3.83
c·HCl	Cl					Cl	CH_3		L	C_2H_5OH	White crystals	245° dec.		$C_{16}H_{13}N_3OCl_2$·HCl	51.84	3.78	51.53	3.98
IXc[d]	Cl					Cl	CH_3	$COCH_3$	M	Ac.	Colorless plates	191–192°		$C_{18}H_{15}N_3O_2Cl_2$	57.46	4.02	57.57	4.20
d	Cl			Cl			CH_3		J	Benz.	Colorless crystals	247–248°	80	$C_{16}H_{13}N_3OCl_2$	57.50	3.92	57.04	4.17
d·HCl	Cl			Cl			CH_3		L	CH_3OH Eth.	Colorless crystals	243–246° dec. 25		$C_{16}H_{13}N_3OCl_2$·HCl	51.84	3.81	51.97	4.16
e	Br					CH_3	CH_3		J	C_2H_5OH	Yellowish prisms	255–256°	41.5	$C_{17}H_{16}N_3OBr$	56.99	4.50	56.92	4.53
IXe	Br					CH_3	CH_3	$COCH_3$	M	Ac.-pet.	Colorless needles	209–210°		$C_{19}H_{18}N_3O_2Br$	57.01	4.53	57.26	4.89
g							CH_3		J	Ac.	Colorless needles	190–191°	69	$C_{16}H_{15}N_3O$	72.43	5.70	72.76	5.52
g·HCl							CH_3		L	CH_3OH-ac. Eth.-pet.	Colorless prisms	225–226°		$C_{16}H_{15}N_3O$·HCl	63.68	5.34	63.58	5.42
h[e]	CH_3						CH_3		K	Ac.	Yellowish prisms	214–215°	50	$C_{17}H_{17}N_3O$	73.09	6.13	73.13	5.94
h·HCl	CH_3						CH_3		L	CH_3OH Ac.-eth.	Colorless prisms	224–225°		$C_{17}H_{17}N_3O$·HCl	64.65	5.75	64.49	6.02
IXh	CH_3						CH_3	$COCH_3$	M	Ac.	Colorless prisms	205–206°		$C_{19}H_{19}N_3O_2$	71.0	5.96	71.16	5.98
i	Br					CH_3			J	Ac.	Yellowish prisms	242–243°	68	$C_{16}H_{14}N_3OBr$	55.183	4.10	56.09	4.30
i·HCl	Br					CH_3			L	CH_3OH Eth.	Colorless prisms	222–223°		$C_{16}H_{14}N_3OBr$·HCl	50.48	3.97	50.78	3.69
i-H[f]	Br						H		J	CH_3OH	White needles	261–262°	66.7	$C_{15}H_{12}N_3OBr$	54.46	3.66	54.84	3.67
i-H·HCl	Br						H		L	CH_3OH Eth.-pet.	Colorless needles	243–244°		$C_{17}H_{12}N_3OBr$·HCl	49.13	3.57	49.38	3.75
IX H i	Br						H	$COCH_3$	M	Diox.	Colorless needles	248–249°		$C_{17}H_{14}N_3O_2Br$	54.85	3.79	54.93	3.94
i-Eth.[g]	Br						C_2H_5		J	Ac.	Yellowish prisms	246–248°	86	$C_{17}H_{16}N_3OBr$	56.99	4.50	56.55	4.44
i-Eth.·HCl	Br						C_2H_5		L	CH_3OH Eth.	Colorless prisms	232–233°		$C_{17}H_{16}N_3OBr$·HCl	51.73	4.34	51.49	4.05
j[e]	CH_3	CH_3				Cl	CH_3		K	CH_3OH	Yellowish prisms	258–259°	50	$C_{18}H_{18}N_3OCl$	6.595	5.53	65.90	5.23
j·HCl	CH_3	CH_3				Cl	CH_3		L	H_2O-C_2H_5OH Eth.	Colorless needles	247–248°		$C_{18}H_{18}N_3OCl$·HCl	59.35	5.26	59.63	5.39

TABLE IV[a] (*continued*)

	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Method	Cryst. from[b]	Color, Shape	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
k[e]	CH_3	CH_3					CH_3		K	Ac.	Yellowish prisms	259–261°	33	$C_{18}H_{19}N_3O$	73.70	6.53	73.31	6.50
k·HCl	CH_3	CH_3					CH_3		L	CH_2OH Ac.	Colorless prisms	230–231°		$C_{18}H_{19}N_3O$·HCl	65.64	6.11	65.46	6.06
IXk	CH_3	CH_3					CH_3	$COCH_3$	M	Ac.-eth.	Colorless prisms	193–194°		$C_{20}H_{21}N_3O_2$	71.62	6.31	71.66	6.23
l						OCH_3	CH_3		J	C_2H_5OH Pet.	Colorless prisms	251–252°	70	$C_{17}H_{17}N_3O_2$	69.13	5.80	69.31	5.51
l·HCl						OCH_3	CH_3		L	CH_3OH Ac.-pet.	Colorless prisms	218–219°		$C_{17}H_{17}N_3O_2$·HCl	61.53	5.47	61.55	5.60
IX l						OCH_3	CH_3	$COCH_3$	M	Ac.	Colorless prisms	181–182°		$C_{19}H_{19}N_3O_3$	67.64	5.68	67.76	5.68
m					OCH_3	OCH_3	CH_3		J	C_2H_5OH Pet.	Yellowish plates	193–194°	63	$C_{18}H_{19}N_3O_2$	66.44	5.89	66.70	5.62
m·HCl					OCH_3	OCH_3	CH_3		L	CH_3OH Ac.-pet.	Yellowish crystals	223–224°		$C_{18}H_{19}N_3O_3$·HCl	59.75	5.57	59.49	5.48

[a] Only substituents other than hydrogen are shown under R_1–R_8. [b] Eth. = ether, pet. = petroleum ether, b.p. 30–60°, ac. = acetone, diox. = dioxane, benz. = benzene. [c] HCl = hydrochloride. The yields were almost quantitative. [d] IX = acetyl derivative. The yields were almost quantitative. [e] In this case also, the normal reaction product VII was isolated [f] H = hydrogen as R_7. [g] Eth. = ethyl group as R_7.

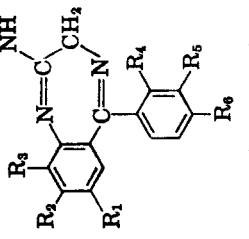
TABLE V[a]. METHYLAMINOMETHYLQUINAZOLINE *N*-OXIDES (VII)



	R_1	R_2	R_3	R_6	Method	Cryst. from[b]	Color, Shape	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
f	CH_3		CH_3		K	CH_2Cl_2 Eth.-pet.	Yellowish prisms	163–165°	52.4	$C_{18}H_{19}N_3O$	73.69	6.53	73.62	6.53
f·HCl	CH_3		CH_3		L	CH_3OH Eth.	Colorless prisms	158–159°	[c]	$C_{18}H_{19}N_3O$·HCl	65.54	6.11	64.89	6.36
h	CH_3				K	Eth. pet.	Yellow needles	113–114°	33	$C_{17}H_{17}N_3O$	73.09	5.13	72.05	5.96
j	CH_3	CH_3		Cl	K	Eth.	Yellowish crystals	139–140°	26	$C_{18}H_{18}N_3OCl$	65.95	5.33	65.74	5.63
j·HCl	CH_3	CH_3		Cl	L	CH_3OH	Yellowish needles	215–216°	[c]	$C_{18}H_{18}N_3OCl$·HCl	59.35	5.26	59.57	5.20
k	CH_3	CH_3			K	Ac. pet.	Yellow needles	135–137°	15	$C_{18}H_{19}N_3O$	73.69	6.53	73.38	6.45

[a] Only substituents other than hydrogen are shown under R_1–R_6. Eth. [b] = ether, Pet. = petroleum ether, b.p. 30–60°, Ac. = acetone. [c] The yield was almost quantitative.

TABLE VI[a]. BENZODIAZEPINES (VIII)



	R_1	R_6	R_7	Method	Cryst. from	Color, Shape	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
c	Cl	Cl	CH_3	N	$CHCl_3$	Colorless plates	241–242°	82	$C_{16}H_{13}N_3Cl_2$	60.39	4.12	59.81	4.57
e	Br	CH_3	CH_3	N	$CHCl_3$	Colorless plates	258–259°	54	$C_{17}H_{16}N_3Br$	59.66	4.71	59.45	4.91
h	CH_3		CH_3	N	CH_2Cl_2	Colorless plates	219°	*ca.* 60	$C_{17}H_{17}N_3$	77.53	6.51	77.67	6.35
i	Br		C_2H_5	N	CH_3OH	Colorless prisms	224°	78	$C_{17}H_{16}N_3Br$	59.66	4.71	59.26	4.42
	Cl[b]		H	N	CH_3OH	Colorless prisms	234–235°	61	$C_{15}H_{12}N_3Cl$	66.79	4.48	66.19	4.39

[a] Only substituents other than hydrogen are shown under R_1-R_7. The corresponding benzodiazepine 4-oxide is described in Paper II.[1]

petroleum ether, colorless prisms or needles melting at 143–145°, which were the hydroxymethoxy derivative (XIV).

Anal. Calcd. for $C_{21}H_{19}O_5NS$: C, 63.46; H, 4.82; CH_3O, 7.81. Found: C, 63.74; H, 4.75; CH_3O, 7.89.

2-Amino-4'-hydroxy-3'-methoxybenzophenone (XVI).[20] A solution of 40 g. of 2-(*p*-toluenesulfonamido)-4'-hydroxy-3'-methoxybenzophenone (XIV) in 200 cc. of concd. sulfuric acid was heated on the steam bath until a sample formed a clear solution on dilution with water (5 min). The mixture was then poured on ice, neutralized with ammonia, and extracted with a mixture of benzene and ether. The extract was dried, concentrated *in vacuo*, and the residue crystallized by the addition of ether or a mixture of benzene and petroleum ether. A total of 14.4 g. of the crystalline reaction product was thus obtained. It was dimorphic and formed after crystallization from a mixture of ether and petroleum ether yellow prisms melting at 99–100° or colorless prisms melting at 112–113°.

Anal. Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; OCH_3, 12.75. Found: C, 68.67; H, 5.14; OCH_3, 12.14.

The negative indo-aniline test[8] of this compound and the toluenesulfanilamido derivative (XIV) indicates that the free hydroxyl group is in position 4'. Treatment with diazomethane in ether solution yielded the known dimethoxy derivative IIIm.

2-Benzamido-3,5-dimethylbenzophenone oxime (XII). A mixture of 45 g. of 2-benzamido-3,5-dimethylbenzophenone (X), 45 g. of hydroxylamine hydrochloride, 90 cc. of pyridine, and 230 cc. of ethanol was refluxed for 16 hr. and then concentrated *in vacuo* with the addition of water. The solid resinous residue was filtered and crystallized by trituration with ether. The yield was almost quantitative. After crystallization from a large amount of ether, the product formed colorless needles melting at 207–208°.

Anal. Calcd. for $C_{22}H_{20}O_2N_2$: C, 76.22; H, 5.85. Found: C, 76.97; H, 5.71.

The alkaline hydrolysis of this compound carried out as in the preparation of XI led to a mixture of XI and the oxime IVf.

2-Aminobenzophenone oximes (IV, Table II). *Method D.* A mixture of 0.25 mole of the 2-aminobenzophenone, 1 mole of hydroxylamine hydrochloride, 220 cc. of pyridine, and 600 cc. of alcohol was refluxed for 24 hr. and then concentrated *in vacuo*. Water was added and the concentration *in vacuo* was continued until most of the pyridine was removed. The residue was dissolved in a mixture of ether or benzene, and water. The organic solution was washed several times with water, dried and concentrated *in vacuo*.[21] The residue was dissolved in ether and yielded, after the addition of petroleum ether, the α-oxime.[22] The mother liquors yielded in some cases an additional crop of a mixture of the two oximes. Fractional crystallization yielded the β-oxime. A mixture of the two oximes gave a melting point depression.

Method E.[23] A mixture of 0.17 mole of the 2-aminobenzophenone, 0.4 mole of hydroxylamine hydrochloride, and 250 cc. of alcohol was refluxed for 15 hr. The solution was neutralized with aqueous sodium carbonate and diluted with 100 cc. of water and 100 cc. of benzene. The precipitated crystals of α-oxime[22] were filtered, the benzene layer was separated, dried, and partly concentrated *in vacuo*, yielding an additional amount of the product. The mother liquors

(21) In some cases the oxime starts to crystallize out before or during the concentration. Addition of petroleum ether leads then to almost quantitative precipitation of the formed oxime.

(22) The α- and β-oxime showed differences in the infrared spectra discussed in paper I of this series[10]. In most cases only the α-oximes were isolated and no further attempts were made to establish the presence of the β-forms.

(23) Method E was only developed at a later stage of these studies and could very probably be used in all cases.

yielded, after dilution with petroleum ether, the β-oxime (IVe).

2-Chloromethyl-4-phenylquinazoline 3-oxides (V, Table III). *Method F.* To a warm solution (50°) of 0.33 mole, of the α-oxime or a mixture of the α-and β-oximes of the 2-aminobenzophenone in 420 cc. of glacial acetic acid was added 0.66 mole of chloroacetyl chloride. The mixture was left at room temperature for 48 hr., saturated with hydrogen chloride gas and concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with ice cold sodium carbonate solution. The organic solution was dried, concentrated to a small volume, and diluted with petroleum ether. The precipitated crystals were filtered. The mother liquor yielded an additional crop. After recrystallisation, the product formed yellow needles.

5-Bromo-2-chloroacetamido-4'-methylbenzophenone α-oxime (XVIIIe) *and 6-bromo-2-chloromethyl-4-(p-tolyl)quinazoline 3-oxide* (Ve, Table III). *Method G.* Into a stirred, cooled (10–15°) solution of 9.15 g. (30 mmoles) of 2-amino-5-bromo-4'-methylbenzophenone α-oxime (IVe) in 45 cc. of dioxane were introduced in small portions 3 cc. (40 mmoles) of chloroacetyl chloride and the equivalent amount of 3*N* sodium hydroxide. The introduction was carried out alternatingly at such a rate as to keep the temperature below 15° and the mixture neutral or slightly alkaline. The reaction was finished after 30 min; the mixture was acidified to *p*H 5, diluted with water, and extracted with ether. The ether extract was dried, concentrated *in vacuo*, and the oily residue was crystallized by the addition of ether. The yield was 8.5 g. (74%). After crystallization from dioxane, the 2-chloroacetamido-5-bromo-4'-methylbenzophenone α-oxime XVIIIe formed colorless prisms melting at 179–180°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2BrCl$: C, 50.35; H, 3.70. Found: C, 50.68; H, 4.02.

A solution of 3 g. of the above compound in 25 cc. of boiling acetic anhydride was cooled to 75° and saturated with hydrogen chloride (15 min.). The mixture was left at room temperature for 30 min., heated again for 2 hr. to 75°, saturated again for 10 min. with hydrogen chloride, and concentrated *in vacuo*. The residue yielding 6-bromo-2-chloromethyl-4-(*p*-tolyl)quinazoline 3-oxide was crystallized. The yield was 25%. This experiment was repeated several times with slight variations, but the yield was not improved. Method F gave still lower yields.

2-Chloromethyl-4-(4'-methoxyphenyl)quinazoline 3-oxide hydrochloride (VI) *and 2-chloroacetamido-4'-methoxybenzophenone oxime* (XVIII l). *Method H.* 2-Amino-4'-methoxybenzophenone oxime (II l) was treated with chloroacetyl chloride according to method F without introduction of hydrogen chloride. The acetic acid solution deposited after 48 hr. the crystalline hydrochloride of the reaction product. It was filtered and formed yellow prisms melting at 175–177°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2Cl_2$: C, 56.99; H, 4.19. Found: 57.28; H, 4.16.

This hydrochloride was worked up with methylene chloride and sodium carbonate as described under method F to yield V-l.

The acetic acid mother liquors were worked up separately according to method F and yielded compound XVIII l. After crystallization from methylene chloride, it formed white prisms melting at 167–169°.

Anal. Calcd. for $C_{16}H_{15}N_2O_3Cl$: C, 60.28; H, 4.74. Found: C, 60.31; H, 4.87.

2-Methylamino-5-phenyl-1,4-benzodiazepine 4-oxides (VI, Table IV). *Method J.* A suspension or solution of 10 g. of the 2-chloromethyl-4-phenylquinazoline 3-oxide (V) in 100 cc. of a 30% solution (wt. by vol.) of methylamine[24] in methanol was stirred at room temperature for 15 hr.[25] The precipitated reaction product (in some cases the product remained in solution) was filtered and the solution containing the rest of the material was concentrated *in vacuo*. The residue was treated with a mixture of ether and an excess of ice cold dilute hydrochloric acid. The ether was discarded, the acidic aqueous solution was made alkaline (with the addition of ice) and the reaction product was extracted with methylene chloride. The solution was dried with sodium sulfate, concentrated *in vacuo*, and the residue was crystallized.

2-Methylamino-5-phenyl-1,4-benzodiazepine 4-oxides (VI) *and 2-methylaminomethyl-4-phenylquinazoline 3-oxides* (VII, Tables IV and V). *Method K.*[26] The reaction was carried out as described under Method J. The less soluble precipitated benzodiazepine derivative VI was filtered after 15 hr.[27] The mother liquors were worked up as under J and yielded after the separation by crystallization of a small amount of admixed "benzodiazepine," the more soluble lower melting quinazoline 3-oxide derivative.[28]

Hydrochlorides of benzodiazepin-4-oxides (VI, Table IV) *and quinazoline 3-oxides* (VII, Table V). *Method L.* To a suspension or solution of the base in the 10–20-fold amount of methanol was added a slight excess of 1*N* methanolic hydrogen chloride. This solution was concentrated *in vacuo* and the residue crystallized.

Acetyl derivatives (IX, Table IV). *Method M.* A solution of the base VI[29] in a mixture of the 5-fold amount of acetic anhydride and the 5-fold amount of pyridine was left at room temperature for 15 hr. and then concentrated *in vacuo*. The residue was dissolved in methylene chloride, the solution washed with ice cold hydrochloric acid and alkali, dried, and concentrated *in vacuo*. The residue was crystallized.

Benzodiazepines (VIII, Table VI). *Method N.* A solution of 1 g. of the benzodiazepine 4-oxide (VI) and 1 cc. of phosphorus trichloride in 25 cc. of chloroform was refluxed for 1 hr., then poured on ice and washed with an excess of ice cold alkali. The organic layer was dried, concentrated *in vacuo*, and the residue crystallized.

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NUTLEY 10, N. J.

(24) For the preparation of the 2-amino compound, i-H, the 30-fold amount of alcoholic ammonia was used, for the 2-ethylamino derivative, i-Eth, the 5-fold amount of alcoholic ethylamine.

(25) In preparing compounds VIb, e, h, and l, the reaction mixture was worked up after 2 hr.

(26) As in most cases no particular attempts were made to isolate compounds of type VII, it is possible that smaller amounts of these isomers were also formed in other cases.

(27) In the preparation of VIh and VIIh no precipitate was formed. The clear reaction mixture was worked up after one hour and the isomers separated by crystallization, the benzodiazepine derivative being considerably less soluble.

(28) On treating Vf with methylamine solution and working up the solution after 2 hr. as under J, only VIIf could be isolated.

(29) For the very little soluble compound VIi-H the 60-fold amount of pyridine and the 10-fold amount of acetic anhydride were used. The acetyl derivative crystallized from the acetylating mixture.